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ORIGINAL ARTICLE

Thyroid dysfunction and anti-thyroid antibodies in Egyptian patients with systemic lupus erythematosus: Correlation with clinical musculoskeletal manifestations☆

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KEYWORDS

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Abstract *Aim of the work:* To study the prevalence of thyroid dysfunction and anti-thyroid antibodies (ATA) in Egyptian patients with systemic lupus erythematosus (SLE), and their association with musculoskeletal manifestations of the disease.

Patients and methods: Cross sectional study included 100 SLE patients and 100 matched controls. Clinical manifestations at any time during disease course were reported. Detailed musculoskeletal examination was done using Ritchie articular index (RAI), 44-Swollen joint count and fibromyalgic tender points. Phalen's test was used to diagnose carpal tunnel syndrome. Free-thyroid hormones (FT3 and FT4), thyroid stimulating hormone (TSH), anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies were measured.

Results: The prevalence of thyroid dysfunction was significantly higher in patients than controls (18% vs. 4%, $p = 0.003$) and all were females. Prevalence of subclinical hypothyroidism (SCHT) and clinical hypothyroidism (CHT) is 10% ($p = 0.002$) and 4% ($p = 0.121$) versus non among controls while, that of subclinical hyperthyroidism (4%) was not significantly different. Prevalence of anti-TPO and anti-TG is higher in patients than controls (35% vs 11%, $p < 0.001$ and 22% vs. 6%, $p = 0.001$). All patients with SCHT had anti-TPO and half of them had anti-TG while all patients

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with CHT had both antibodies. Hypothyroidism was associated significantly with aging ($p = 0.01$), longer disease duration ($p < 0.001$), high BMI, high RAI scores, arthritis, positive Phalen's test and fibromyalgia ($p < 0.001$ for all) in comparison to euthyroid patients.

Conclusion: Hypothyroidism was more prevalent in SLE patients and its detection is recommended to reduce the risk of musculoskeletal related morbidity.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multifaceted inflammatory disease often associated with other organ-specific autoimmune diseases [1]. Autoimmune thyroiditis is an organ-specific disease and its association with thyroid dysfunction and SLE was reported in several studies and yielded conflicting conclusions. While some studies reported higher prevalence of hypothyroidism in SLE patients others reported higher prevalence of hyperthyroidism [2–8]. The association between thyroid dysfunction and SLE was first reported by White et al. [9] and Hijmans et al. [10] in 1961, who showed that the thyroid dysfunction appeared more common in SLE than in general population. Thyroid involvement being non-life-threatening than other organ involvement in SLE, it is often underestimated and passes undetected for long contributing to the morbidity of the illness. So, it is important to diagnose the thyroid dysfunction in lupus patients and to treat them accordingly [2]. The aim of this study was to estimate the prevalence of thyroid dysfunction and anti-thyroid antibodies in Egyptian SLE patients and their association with the musculoskeletal manifestations of the disease.

2. Patients and methods

2.1. Patients

A cross sectional case–control study included 100 Egyptian SLE patients who met the American College of Rheumatology Classification criteria of SLE [11,12] with age more than 18 and had at least 5-year disease duration and 100 age and sex matched apparently healthy individuals served as control. The patients were recruited from the Maadi Armed Force Hospital during the period from October 2011 till October 2012. Demographic data and clinical manifestations at any time during the disease course were reported for all patients. Patients with thyroid disease, thyroid medications or thyroidectomy were excluded from the study. All participants provided written informed consent prior to their inclusion. This study was approved by the local ethics committees and in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

Full history taking and clinical examination were done taking into consideration the symptoms and signs of thyroid dysfunctions. Detailed musculoskeletal examination was done. Assessment of joint tenderness was done using the Ritchie articular index (RAI), 53 joints in 26 units, graded according to tenderness on pressure (0 = no pain; 1 = patient complains of pain; 2 = patient complains of pain and winces; 3 = patient complains, winces, and withdraws; maximum score 78) [13]. Assessment of joint swelling was done using the 44-Swollen joint count [14]. Fibromyalgic tender points were scored for each patient [15]. Phalen's test was used to diagnose clinically the carpal tunnel syndrome. This test was considered positive if there were paraesthetic symptoms along the cutaneous distribution of median nerve after maintaining maximal wrist flexion for one minute [16].

2.2. Laboratory investigations

Routine laboratory investigations for patients with SLE were done including complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum alanine transaminase (ALT), aspartate transaminase (AST), creatinine, complete urine analysis, 24 h urinary proteins, C3 and C4, anti-nuclear antibody (ANA), and anti-double stranded DNA (anti-ds-DNA).

2.2.1. Thyroid hormones and thyroid stimulating hormone (TSH) measurements

The sera were examined for free triido thyronine (FT3), free thyroxine (FT4) and TSH by micro-particle enzyme immunoassay. The normal reference range for FT3 is 1.8–4.6 pg/ml, for FT4 is 1.0–1.8 ng/dl and for TSH is 0.3–4.2 μIU/ml according to Bemben et al. [17] and Bell et al. [18]. Elevated TSH with low thyroid hormones was categorized as clinical hypothyroid (CHT), while those with high TSH with normal thyroid hormones were considered as subclinical hypothyroid (SCHT). Similarly, low TSH with raised thyroid hormones and normal thyroid hormones was called clinical hyperthyroid and subclinical hyperthyroid, respectively [2].

2.2.2. Anti-thyroid antibodies (ATA) measurements

Serum anti-thyroglobulin antibodies (anti-TG) and anti-thyroid peroxidase antibodies (anti-TPO) were measured by immune-metric assays. Antibodies were considered positive if levels were >1 IU/ml for anti-TG and >50 IU/ml for anti-TPO.

Statistical analysis: Data entry, processing and statistical analysis were carried out using Statistical Package for the Social Sciences version 20 (SPSS Inc., USA). Data were reported as mean ± standard deviation (SD). Tests of significance (student *t*-test, Chi-square test with Fisher's exact test, and Yates correction were used when appropriate) were used to compare between different groups. *p* values <0.05 was considered to be statistically significant.

Table 1 Demographic, clinical manifestations and laboratory tests of lupus patients.

Demographic, clinical manifestations at any time of the disease course and laboratory tests	Number (%)
Demographic data	
Mean age (years) ± SD	38.5 ± 13.5
Female/male (ratio)	9:1
Disease duration (years) ± SD	12 ± 6.3
Clinical manifestations	
Malar rash	65 (65%)
Discoid rash	13 (13%)
Photosensitivity	72 (72%)
Oral ulcers	63 (63%)
Arthritis/arthralgia	92 (92%)
Serositis	
Pleuritis	31 (31%)
Pericarditis	14 (14%)
Nephritis	28 (28%)
Neurologic	
Seizures	2 (2%)
Headache	3 (3%)
Psychiatric (depression)	2 (2%)
Laboratory	
Anemia	35 (35%)
Leukopenia	39 (39%)
Thrombocytopenia	14 (14%)
ANA	97 (97%)
Anti ds-DNA	94 (94%)
Anti-Sm antibodies	15 (15%)

ANA, antinuclear antibody.

3. Results

3.1. SLE manifestations

Demographic data, clinical manifestations and laboratory tests of SLE patients were shown in Table 1. Arthritis/arthralgia, photosensitivity, malar rash, oral ulcers, serositis and nephritis were found to be the most frequent clinical manifestations and the neuro-psychiatric manifestations were the least frequent.

3.2. Mean serum level of free-thyroid hormones, TSH and ATA among patients and controls

Although, the mean serum level of FT3, FT4 and TSH was within normal range among patients, but they were statistically elevated in comparison to controls ($p < 0.001$ for all). The mean serum anti-TPO and anti-TG antibodies levels were higher than the normal range and were statistically elevated ($p < 0.001$ for both) among patients in comparison to controls, as shown in Table 2.

3.3. Prevalence of thyroid dysfunction among patients and controls

According to thyroid hormones and TSH levels, we had 82 (82%) patients with euthyroid state versus 96 (96%) among the control group ($p = 0.002$). Accordingly, we had 18 (18%) patients with thyroid dysfunction versus 4 (4%) among the control group ($p = 0.003$). Patients with thyroid dysfunction were classified into 10 (10%) patients with SCHT versus none of controls ($p = 0.002$), 4 (4%) patients with clinical hypothyroidism (CHT) versus none of controls ($p = 0.121$), and 4 patients with subclinical hyperthyroidism versus 4 among controls. All patients with thyroid dysfunction were females.

3.4. Prevalence of ATA among patients and controls

Anti-TPO antibody was detected in 35 (35%) patients versus 11 (11%) among the controls ($p < 0.001$). Anti-TG antibody was detected in 22 (22%) patients versus 6 (6%) among the controls ($p = 0.001$). Both antibodies were found together in 20 (20%) patients. Anti-TPO antibody was found in all patients with SCHT and all patients with CHT in contrast to none of the controls ($p = 0.002$, $p = 0.121$ respectively). Anti-TG antibody was found in 5 (50%) patients with SCHT and in all patients with CHT in contrast to none of the controls ($p = 0.059$, $p = 0.121$ respectively). Among patients with euthyroid state (82 patients), 21 (25.6%) had anti-TPO antibody and 13 (15.85%) had anti-TG antibody versus 11% and 6% among controls respectively ($p > 0.05$ for both). Patients and controls with subclinical hyperthyroidism had no anti-thyroid antibody.

It was found that patients with anti-TPO and anti-TG antibodies had statistically elevated TSH levels ($p < 0.001$) in comparison to those without antibodies. FT3 and FT4 levels showed no significant differences among patients with and without either of antibodies. This is shown in Table 3.

3.5. The relation between thyroid status and age, disease duration and BMI

SCHT and CHT were found to be significantly associated with aging ($p = 0.01$, $p = 0.02$ respectively) and longer disease duration ($p < 0.001$ for both) and associated with high BMI ($p < 0.001$ for both) in comparison to euthyroid patients.

Table 2 Levels of thyroid hormones, TSH and anti-thyroid antibodies in SLE patients and controls.

Parameters	SLE	Control (No. 100)	*p* Value (No. 100)
FT3 (pg/ml)	3.2 ± 1.2	1.83 ± 0.56	0.000
FT4 (ng/dl)	1.9 ± 0.6	1.28 ± 0.28	0.000
TSH (μIU/ml)	3.5 ± 1.4	1.92 ± 0.82	0.000
Anti-TPO (IU/ml)	75 ± 13.8	45 ± 2.7	0.000
Anti-TG (IU/ml)	2.2 ± 0.4	0.8 ± 0.3	0.000

$p < 0.000$, very highly significant.

Table 3 Thyroid hormone and TSH levels among patients with and without antithyroid antibodies.

Parameter	SLE with anti-TPO antibodies ($N = 35$)	SLE without anti-TPO antibodies ($N = 65$)	p Value
FT3 (pg/ml)	1.1 ± 0.35	1.22 ± 0.21	NS
FT 4 (ng/ml)	1.1 ± 0.24	1.21 ± 0.52	NS
TSH (μIU/ml)	3.43 ± 1.7	1.62 ± 0.75	0.000
	SLE with anti-TG antibodies ($N = 22$)	SLE without anti-TG antibodies ($N = 78$)	p Value
FT3 (pg/ml)	1.52 ± 0.32	1.31 ± 0.54	NS
FT 4 (ng/ml)	1.31 ± 0.54	1.41 ± 0.25	NS
TSH (μIU/ml)	4.35 ± 1.9	1.81 ± 0.8	0.000

$p < 0.000$, very highly significant.

Table 4 Comparison between SLE patients according to the thyroid state regarding age, BMI and disease duration.

Parameters	Euthyroid $N = 82$	SCHT $N = 10$	CHT $N = 4$	Subclinical hyperthyroid $N = 4$	p Value		
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	$p1$	$p2$	$p3$
Age (years)	28.1 ± 13	39.4 ± 16.2	44.2 ± 20.8	35.5 ± 12.4	0.01	0.02	NS
BMI (kg/m^2)	26.4 ± 1.4	28.4 ± 2.3	31.4 ± 3.3	21.4 ± 1.3	0.000	0.000	0.000
Disease duration (years)	7.5 ± 2.6	12.0 ± 6.3	17.5 ± 1.5	8.5 ± 0.6	0.000	0.000	NS

BMI, body mass index; SCHT, subclinical hypothyroidism; CHT, clinical hypothyroidism; $p1$: SCHT vs. euthyroid; $p2$: CHT vs. euthyroid; $p3$: subclinical hyperthyroid vs. euthyroid; $p < 0.05$, significant; $p < 0.000$, very highly significant.

Subclinical hyperthyroid patients were associated with significant reduction in BMI in comparison to euthyroid patients, as shown in Table 4.

3.6. Musculoskeletal manifestations of SLE and thyroid dysfunctions

Different musculoskeletal manifestations were compared in lupus patients with different thyroid dysfunctions against those with euthyroid state as shown in Table 5. Ritchie-articular index with score $\geqslant 5$ was found in 9 patients with SCHT versus 7 with euthyroid state (90% vs. 8.5%, $p < 0.001$), polyarthritis and fibromyalgia were found in 10 for each versus none (100% vs. 0%, $p < 0.001$) and positive Phalen's test was found in 8 versus none (80% vs. 0%, $p < 0.001$).

Comparing patients with CHT against those with euthyroid state revealed that Ritchie-articular index with score $\geqslant 5$ was found in 4 patients with CHT versus 7 with euthyroid state (100% vs. 8.5%, $p < 0.001$), oligoarthritis/polyarthritis was found in 3 versus none (75% vs. 0%, $p < 0.001$), fibromyalgia and positive Phalen's test were found in 4 for each versus none (100% vs. 0%, $p < 0.001$).

On comparing patients with subclinical hyperthyroidism against those with euthyroid state, it was found that a significant Ritchie-articular index with score $\geqslant 5$ in 3 among the former group versus 7 among the latter group (75% vs. 8.5%, $p < 0.001$) and monoarthritis/oligoarthritis in 4 versus none in the latter group (100%, $p < 0.001$). None of patients with subclinical hyperthyroidism had fibromyalgia or positive Phalen's test.

4. Discussion

While thyroid diseases and thyroid antibodies are not included in the lupus classification criteria, it is realistic to investigate whether patients with SLE have higher prevalence of thyroid disease than that in the general population [19]. However,

Table 5 Musculoskeletal signs in SLE patients according to the thyroid state.

Parameter	Euthyroid $N = 82$	SCHT $N = 10$	CHT $N = 4$	Subclinical hyperthyroid $N = 4$	p Value			
					$p1$	$p2$	$p3$	
RAI/53	0	53	0	0	0	–	–	–
	1–4	22	1	0	1	0.6	–	0.6
	5–10	7	8	2	2	0.000	0.000	0.000
	11–22	0	1	2	1	0.000	0.000	0.01
Swollen joints/44	0	82	0	1	0	–	–	–
	1–4	0	0	2	4	–	0.000	0.000
	$\geqslant 5$	0	10	1	0	0.000	0.000	–
Fibromyalgia	Positive	0	10	4	0	0.000	0.000	–
Phalen's test	Positive	0	8	4	0	0.000	0.000	–

RAI, Ritchie-articular index; $p = 0.01$, highly significant; $p < 0.000$, very highly significant.

divergence still exists in relation to the prevalence and still a matter of controversy.

The prevalence of thyroid dysfunction was significantly more among lupus patients than controls (18% vs. 4%, $p = 0{,}003$). Hypothyroidism was more common than hyperthyroidism (14% vs. 4%). SCHT (10%) was the most common thyroid dysfunction in our lupus patients followed by CHT (4%). Although SCHT and CHT were not detected in the controls, the former only showed a significant prevalence in comparison to controls ($p = 0.002$) and the latter did not show ($p > 0.05$). This might be related to their small number. Subclinical hyperthyroidism was present in 4% of lupus patients as well as the controls. Previous studies showed discrepancies in relation to the thyroid dysfunction types which are more commonly met [2]. While our results regarding the prevalence of SCHT and CHT came in agreement with previous studies [2,20–23], they showed a higher prevalence when compared to lupus cohort of another studies [24–28] or lower prevalence when compared to others [29,30].

ATA levels were significantly elevated in lupus patients in comparison to controls ($p < 0.001$). ATA were found in 37% of lupus patients, in accordance with Boey [26]. On the other hand, our ATA results were much lower [29,31,32] or higher in contrast to others [33,34]. Anti-TPO was present in 35% of lupus patients and this prevalence was found to be higher [23,35] or lower than others [36]. In addition, anti-TG was found in 22% of our lupus patients which came in accordance with the study of Chan et al. [20]. On the other hand, our anti-TG prevalence was higher [23,36] or lower than others [35,37]. Eleven percent of our controls were positive for anti-TPO which came in accordance with earlier studies [23,38] or higher than others [39,40].

All patients (18%) with thyroid dysfunction were females and had autoimmune thyroid disease being positive to one or both ATA. Anti-TPO was detected in all patients with SCHT and CHT while anti-TG was found in half of SCHT and all CHT patients. Patients with subclinical hyperthyroidism were negative for both ATA. Among euthyroid patients, anti-TPO was found in 25.6% and anti-TG was found in 15.85%.

According to the Nordyke and coworkers [41], and Diaz and Lglesias [42], SCHT can change into CHT. This change was found to be associated with aging, female gender and with positive ATA [20,43,44]. Accordingly, follow up of our SCHT patients may with time (i.e. aging) show this change into CHT, especially that all our lupus patients with SCHT are females and have positive ATA. It is also possible that our euthyroid patients, especially the females who have positive ATA, may through the next coming years (i.e. aging) develop SCHT or CHT. Our study showed that the hypothyroidism, either SCHT or CHT, was associated with aging and longer disease duration and all of them were females and had ATA in accordance to previous mentioned studies [20,43,44].

Patients with ATA had a significant increased TSH level than those without ATA ($p < 0.001$). This appeared to be logic because most patients with ATA had hypothyroidism (14/20, 70%) and this is usually associated with increased level of TSH as a part of the hypothyroid diagnosis [45].

In the present study, we tried to discover how different lupus musculoskeletal manifestations were affected by thyroid dysfunction. Ritchie-articular index score was found to be significantly elevated in patients with SCHT, CHT ($p < 0.001$) and subclinical hyperthyroid ($p < 0.01$) in comparison to patients with euthyroid state. Moreover, swollen joint count was found to be significantly elevated in patients with SCHT and CHT ($p < 0.001$) compared to the euthyroid patients. Polyarthritis in particular, was significantly associated with SCHT ($p < 0.001$), while monoarthritis/oligoarthritis was significantly associated with CHT ($p < 0.001$). Fibromyalgia was a common companion of lupus and has a considerable impact on morbidity [46]. It was detected in 14% of our patients, all of them had hypothyroidism and of highly significant result in comparison to the euthyroid patients. This was a little bit lower than previous studies [47,48]. Finally, positive Phalen's test for diagnosing carpal tunnel syndrome was found in 12% of patients and all had hypothyroidism with very high statistical significant difference ($p < 0.001$) compared to the euthyroid patients.

It can be concluded that hypothyroidism is more often seen in lupus patients than normal population and significantly associated with the musculoskeletal manifestations of the disease especially the Ritchie-articular index, arthritis, fibromyalgia and Phalen's test. Thyroid function tests and ATA should be done in all lupus patients, as their assessment may add benefit to reduce the risk of musculoskeletal related morbidity.

Conflict of interest

None of the authors have any potential financial or personal conflict of interest related to this manuscript.

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